Classification of More-than-Minimally Manipulated (MMM) Allograft Heart Valves

Circulatory System Devices Panel Meeting

October 9, 2014

Presentation by:

Office of Device Evaluation (ODE) and Office of Science and Biometrics (OSB)
Center for Devices and Radiological Health (CDRH)
U.S. Food and Drug Administration

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FDA Classification Team

Device Review Team

- Diane Nell, Ph.D.
- Steven Kurtzman, M.D.

Systematic Literature Review

- Helen (Hongying) Jiang, Ph.D.

MAUDE Search

- Jenny (Chih-hsin) Liu, RN, MSN

Purpose of Panel Meeting

The purpose of this panel meeting is to discuss the classification of MMM allograft heart valves, which are regulated as medical devices in CDRH, for use in heart valve replacement procedures.

The panel will be asked to make recommendations regarding the regulatory classification of these currently unclassified devices.

Current Regulatory Oversight

- Allograft (human) heart valves:
  - Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) regulated solely under Section 361 of the PHS Act and the "tissue rules" (21 CFR Part 1271)

- Prosthetic heart valves (mechanical, bioprosthetic):
  - regulated as devices CDRH
  - Class III (PMA devices)

- MMM allograft heart valves:
  - regulated as devices in CDRH
  - *Presently unclassified, regulated under 510(k)* – subject of this meeting

Device Description

- MMM allograft heart valve:
  - Human heart valve subjected to processing which alters the original relevant characteristics of the tissue relating to its utility for reconstruction, repair, or replacement
  - e.g., CryoValve SG Pulmonary Human Heart Valve (K033484)
  - Not sterilized

- As each new technology for manufacturing allograft heart valves is developed
  - Consider whether all of the criteria for regulation solely under section 361 are met (i.e., if considered a “tissue”)

Device Description (continued)

- Processing may impact:
  - Hydrodynamic performance
  - Structural integrity
  - Durability
  - Immunogenicity
- Processing methods may:
  - Vary across manufacturers
  - Evolve/change over time

Device Description (continued)

- Novel technology – e.g., decellularization …
- No standards/well-established scientific methods …
  - to evaluate decellularization processes
  - to conduct *in vitro* evaluation (tissue properties, durability)
  - to evaluate *in vivo* recellularization
- Important safety and effectiveness concerns:
  - incomplete or variable decellularization (affecting antigenicity and calcification)
  - limited *in vivo* recellularization (affecting valve structural integrity and dimensional stability)
  - extracellular matrix structural deterioration

Regulatory History

- One (1) clearance from one (1) manufacturer

Manufacturer	Device Name	510(k) Number
CryoLife, Inc.	CryoValve® SG Pulmonary Human Heart Valve (Model SGPV10) and CryoValve® SG Pulmonary Human Heart Valve and Conduit (Model SGPV00)	K033484 K083106 (revised description to include immunogenicity claim) K092021 (extended shelf life)

- Clearance through 510(k) based on comparison to preamendments[1] device (non-MMM allograft heart valves)
  - Note: As of May 25, 2005, allograft heart valves that meet all criteria for regulation as tissue products under section 361 of the PHS Act are no longer regulated as devices in CDRH.

[1] For more information regarding requirements to demonstrate preamendment status, please refer to http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ComplianceActivities/ucm072746.htm

Proposed Classification

Class III

- Life-sustaining devices
- Insufficient information to establish special controls
- Known risks cannot be adequately controlled by general and special controls

Risks to health are consistent with other, non-allograft replacement heart valves (Class III)

Representative Indications for Use

"[This device] is indicated for the replacement of diseased, damaged, malformed, or malfunctioning native or prosthetic [position] valves."

Clinical Background

Clinical Background

Steven Kurtzman, M.D.
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Office of Device Evaluation
Center for Devices and Radiological Health

Heart Valve Disease

- Prevalence: > 5 million Americans diagnosed annually
- Aortic and mitral valve disease most prevalent
- Treatment options
  - Medical management
  - Surgical or transcatheter valve repair
  - Surgical replacement with prosthetic valve or autograft
  - Implantation of transcatheter prosthetic valve

Heart Valve Replacement

- Open-heart surgery (full sternotomy, mini-sternotomy, mini-thoracotomy)
- Cardiopulmonary bypass
- Surgery 3 to 6 hours long
- 3 to 10 days in hospital
- Recovery at home: 6 to 8 weeks post-procedure, or 1 to 4 weeks for minimally-invasive procedures
- Outpatient Cardiac Rehabilitation: 12 weeks

Intended Patient Population for Allografts

- Mostly used in young patients with complex heart disease:
  - offer advantage over porcine bioprosthetic valves which have high rate of structural valve dysfunction due to accelerated calcification
  - offer advantage over mechanical valves which require anticoagulation
  - available in smaller sizes than prosthetic heart valves
- Also used in young adults and less often used in older adults

Intended Patient Population for Allografts

- Pulmonary allograft valves used for:
  - Right ventricular outflow tract (RVOT) reconstruction
  - Ross Procedure to replace pulmonary autograft used for aortic valve replacement
- Aortic allograft valves implanted less frequently than pulmonary allograft valves
- Estimated < 2,000 allograft implants per year

MMM Allograft Valve Risks to Health

- Similar to risks to health for non-allograft prosthetic heart valves
- Except MMM allografts have added risk of immunogenicity and possibly increased infection since these are non-sterile devices

Systematic Literature Review

Systematic Literature Review

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Center for Devices and Radiological Health

Methods: Databases and Terms

Search 1:

"allograft heart valves" or "cryovalve" or "synergraft"

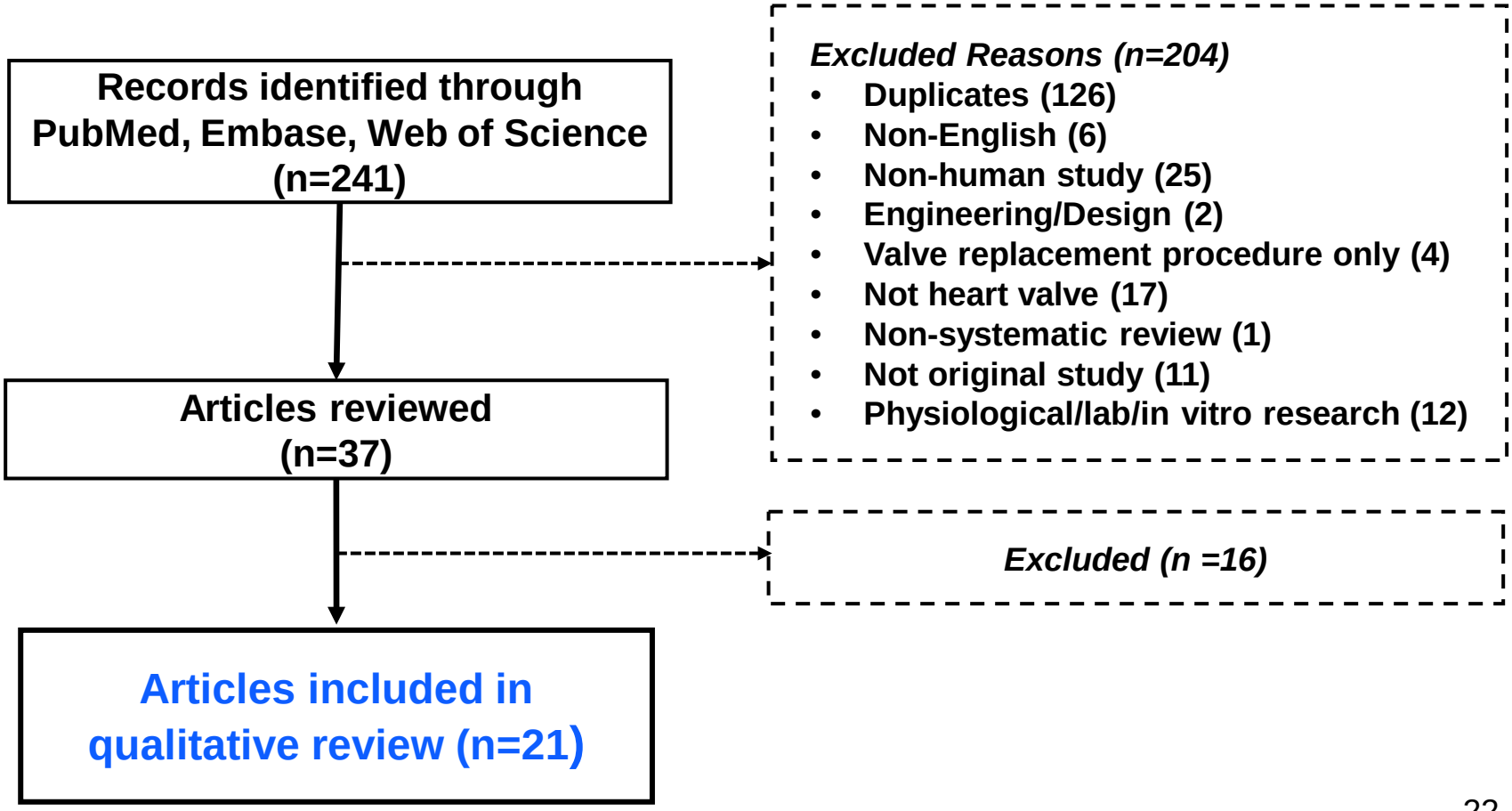
Search 2:

"homograft heart valve" NOT ("allograft heart valves" or "cryovalve" or "synergraft")

Databases: PubMed, Embase, and Web of Science

Time periods: 1/1/1990 to 9/29/2014

Methods: Article Selection



Results

- Study design: No RCTs, prospective =10, retrospective =11
- Population: infant to 80 years old
- Location: US =12; OUS =9
- Study Sponsor: company = 5-6
- Valve positions:
  - pulmonary only =13
  - pulmonary and aortic =7
  - aortic only =1
- Valves: SG vs SA =11, SG-only =3, SA-only =7

(SG: SynerGraft decellularized; SA: standard allograft heart valve)

Results

The 14 SG studies:

- Sample sizes: 11-342
- Follow-up times (mean or median, yr): 0.3-5.7

First author /year	Sample Size	F/U time (mean/median or max, yr)	First author/year	Sample Size	F/U time (mean/median or max, yr)
Dohmen 2007	11	3.8	Tavakkol 2005	26	1.4
Hawkins 2003	14	1	Brown 2011	29	4.9
Sievers 2003	17	>0.5	Ruzmetov 2012	39	5.7
Bechtel 2004	22	0.8	Konuma 2009	41	3.8
Zehr 2005	22	2.5	Burch 2010	47	5.5
Bechtel 2008	23	4.3	Elkins 2001	66	0.3
Bechtel 2003	24	0.5	Brown 2010	342	4

Results

- **Safety**:

Adverse Events	Rates (%)
Death or valve-related death	0-15%
Endocarditis or infection	0-2%
Thromboembolism/thrombus/bleeding	0-1%
Re-intervention/re-operation	4-19%
Valve/conduit deterioration/dysfunction	0-26%
Calcification	0-26%
Explant	2-19%
Fibroproliferation	42%

Results

- **Effectiveness**:
  - Mean and peak pressure gradients increased in 4 articles: 2 clinically significant, 2 not clinically significant
  - Effective orifice area (EOA) demonstrated a mild decrease over 6 mo, not clinically significant
  - Valve regurgitation: did not change clinically significantly or did not occur at up to 5 yr follow-up in 3 studies

- **Immune responses**
  - maintained low (i.e., <10%) positive immune response at up to 12 mo follow-up

Limitations

- Financial conflict of interest: ~6/9 (~67%) US studies were funded by the Sponsor
- Small sample size: 71% of the articles had <50 patients per device type
- Immunology findings differ by:
  - Valve positions
  - Patient populations
  - Detection techniques of immunogenicity

Reports on Other MMM Products

Reports on Other Decellularized Products

Diane Nell, Ph.D.
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Reports on Other Decellularized Devices

- Simon *et al.* (2003) – decellularized porcine heart valve implanted in 4 children (2.5 – 11 yrs) in RVOT; 3 died within 1 year due to structural failure or rapid degeneration; fourth was prophylactically explanted; all 4 valves showed severe inflammation

- Madden *et al.* (2005) - decellularized femoral vein allografts - significantly more access graft failures (i.e., 30% failed in the decellularized cohort versus 18% in the PTFE cohort)

- Sharp *et al.* (2004) - decellularized bovine ureter used as a femoral-posterior tibial bypass graft in a 68-year-old patient. The article reported: "Our patient [presented] at 8 weeks with aneurismal degeneration along the course of the graft

- Stam *et al.* (2004) - cell removal impairs the physical properties of the valve structure (porcine aortic valves) and exposes bare collagen fibers that are highly thrombogenic

Reports on Other Decellularized Devices

- MMM processing can have global impact on structural integrity of allograft tissue
- Concerns for increased risks of:
  - Structural valve deterioration
  - Aneurismal degeneration (of conduit portion)
  - Thrombus/thromboembolism
  - Stroke
  - Renal insufficiency/failure

MAUDE Search

Manufacturer and User Facility Device Experience (MAUDE) database

Medical Device Reports (MDRs)

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Manufacturer and User Facility Device Experience (MAUDE) database

Strength of MDR Data

- Qualitative snapshot
- "Real world"
- Rare/unexpected events
- Long term events
- Vulnerable patient population
- Off-label use
- Use errors

Limitations of MDR Data

- Under-reporting
- Insufficient information
- Causality not confirmed
- Reporting bias
- Lack of device usage data
- Cannot calculate rates of events
- Trends should be interpreted cautiously

Search Methods & Results

- **MAUDE database searched by –**
  - **Date Report Received ≤ Sep, 28, 2014 and**
  - **Manufacturer name (CryoLife) and**
  - **Brand name (SynerGraft or SG valve), or model/catalog number (SG)**
- **Results--**
  - **60 MDRs ➔ 58 MDRs***
    - **31 MDRs (pulmonary): 2 death events**
    - **27 MDRs (aortic)**

***Two duplicate reports were excluded**

MAUDE Search – Pulmonary Valve (31 MDRs)

Reported Problem	Count	Time to Event Occurrence (TTEO)			
		<1 day	1 day – 1 year	1 year – 11 years	Not Reported
*Structural Problems	18	10	3	4	1
Infection/Endocarditis	6	0	3	2	1
Reaction	2	0	2	0	0
Mass	2	0	2	0	0
Incorrect Size	2	2	0	0	0
Aneurysm	1	0	1	0	0

*The structural problems include cuts, holes, tears, rips, cracks, splits, incompetence, degradations, plaques, calcification of the device, valve stenosis or regurgitation/insufficiency.

MAUDE Search – Aortic Valve (N=27 MDRs)

Reported problem	Count	TTEO			
		<1 day	1 day - 1 year	1 year - 11 years	Not Reported
Structural Problem	25	4	2	18	1
Infection	1	0	1	0	0
Bleeding	1	1	0	0	0

Summary of MDRs

- The structural problems were the most frequently reported events for both SG Pulmonary and Aortic HV.
- Two deaths associated with structural problems of the SG Pulmonary HV were reported.
- The relationships between the “Reaction/scarring” and “Mass” events and the SG Pulmonary HV remained unclear.

Summary

Summary & Proposed Classification

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Proposed Classification

Section 513(a)(1)(C)

(C) CLASS III, PREMARKET APPROVAL.—A device which because—

- (i) it (I) cannot be classified as a class I device because insufficient information exists to determine that the application of general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, and (II) cannot be classified as a class II device because insufficient information exists to determine that the special controls described in subparagraph (B) would provide reasonable assurance of its safety and effectiveness, and

- (ii)(I) is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or

- (II) presents a potential unreasonable risk of illness or injury,

Proposed Classification

Class III

- Insufficient information … (513(a)(1)(C)(i))
- Life-sustaining devices … (513(a)(1)(C)(ii))

or

- Potential unreasonable risk of illness or injury … (513(a)(1)(C)(iii))

Insufficient Information

- Only 1 cleared MMM allograft heart valve (K033484)
- Literature limitations (no RCTs, small sample sizes, etc.)
- No standards:
  - To evaluate decellularization processes
  - To conduct *in vitro* evaluations (e.g., durability)
  - To evaluate *in vivo* recellularization
- e.g.,
  - Methods of decellularization are varied (e.g., chemical, heat, physical) and not established (can impact uniformity and consistency in cellularity)
  - Methods for quantification of decellularization are varied (e.g., DNA/RNA assays, lipid assays, histologic and fluorescent microscopy staining) and not established – method accuracy is important for monitoring process and assessing impact of process changes; is the associated parameter clinically meaningful (regarding impact on antigenicity), and how sensitive is patient immune response to remaining cellular debris?

Insufficient Information

- Only 1 cleared MMM allograft heart valve (K033484)
- Literature limitations (no RCTs, small sample sizes, etc.)
- No standards/well-established scientific methods:
  - To evaluate decellularization processes
  - To conduct *in vitro* evaluations (e.g., mechanical properties, durability)
  - To evaluate *in vivo* recellularization

The panel will be asked to address the sufficiency of information to establish special controls.

Life-Sustaining Devices

- Life-sustaining devices:
  - Replace malfunctioning native or prosthetic valves
  - Control flow of blood throughout heart
  - Proper functioning is critical to life of patient

Risks to Health

- Risk to health:
  - A direct risk associated with the use of the device
- Adverse Event:
  - A potential clinical consequence of the risk
- Example (risk → adverse event):
  - Structural valve deterioration → death
  - Thrombus/thromboembolism → stroke

Risks to Health

Risks:

- Structural valve deterioration
- Nonstructural dysfunction
- Thrombus / thromboembolism
- Allosensitization, rejection, other immune responses
- Infection
- Regurgitation
- Stenosis
- Hemolysis
- Hemorrhage

Adverse Events:

- Death
- Stroke
- Pulmonary embolism
- Heart failure
- Angina
- Myocardial infarction
- Endocarditis
- Renal insufficiency/ failure
- Reoperation
- Explantation

The panel will be asked to address the completeness of the risks to health noted above.

Manufacturing

- Known risks cannot be adequately controlled by general and special controls, because …
  - Manufacturing review is necessary, as MMM processing has global effect on valve tissue (recall the device description: “Human heart valve subjected to processing which alters the original relevant characteristics of the tissue …”), impacting:
    - Hydrodynamic performance
    - Structural integrity
    - Durability
    - Immunogenicity
  - Review of supplemental changes is necessary

Manufacturing

- Known risks cannot be adequately controlled by general and special controls, because …
  - Manufacturing review is necessary, as MMM processing has global effect on valve tissue (recall the device description: "Human heart valve subjected to processing which alters the original relevant characteristics of the tissue …"), impacting:
    - Hydrodynamic performance
    - Structural integrity
    - Durability
    - Immunogenicity
  - Review of supplemental changes is necessary

Reserved for Class III devices

Necessary Controls

Due to …

- Life-sustaining devices
- Impact of MMM processing (which alters original relevant characteristics of tissue)
- Relative novelty of MMM processing
- Potential variability of MMM processing
  - Across manufacturers
  - Over time

Necessary Controls

- Premarket review of manufacturing information
- Pre-approval inspections
- Review of site changes
- Postmarket review of significant manufacturing changes
- Annual reporting

	510(k)	510(k) w/Special Controls	PMA
Bench Testing	✓	✓	✓
Animal Studies	✓	✓	✓
Clinical Trials	510(k) integrity inspection only if FDA finds a “due cause". Information kept on file by sponsor-open for inspection if product issue	510(k) integrity inspection only if FDA finds a “due cause". Information kept on file by sponsor-open for inspection if product issue	PMA pivotal sites undergo BIMO inspections for integrity and assessment of sponsor quality/GCP over site
Premarket review of manufacturing			✓
Pre-approval inspection			✓
Postmarket review of changes in manufacturing facilities location			✓
Postmarket review of significant manufacturing process changes			✓
Postmarket surveillance options	522 Postmarket Surveillance Studies	522 Postmarket Surveillance Studies	Post-Approval Studies and Postmarket Surveillance Studies
Annual Reporting			✓

Conclusion

Our recommendation is to classify MMM allograft heart valves for use in heart valve replacement procedures as **Class III** devices requiring submission of a PMA

(all other replacement heart valves in CDRH are Class III)

The panel will be asked to comment on the classification recommendation for MMM allograft heart valves in heart valve replacement procedures.

Representative Indications for Use

"[This device] is indicated for the replacement of diseased, damaged, malformed, or malfunctioning native or prosthetic [position] valves."

Thank You

Questions?

Questions for Panel

1. FDA has identified the following risks to health for MMM allograft heart valves based upon literature and the Manufacturer and User facility Device Experience (MAUDE) database.

Risks:

- Structural valve deterioration
- Nonstructural dysfunction
- Thrombus / thromboembolism
- Allosensitization, rejection, other immune responses
- Infection
- Regurgitation
- Stenosis
- Hemolysis
- Hemorrhage

A. Do you agree with inclusion of all of these risks in the overall risk assessment of MMM allograft heart valves?

B. Do you believe that any additional risks should be included in the overall risk assessment of MMM allograft heart valves?

Risks to Health

Risks:

- Structural valve deterioration
- Nonstructural dysfunction
- Thrombus / thromboembolism
- Allosensitization, rejection, other immune responses
- Infection
- Regurgitation
- Stenosis
- Hemolysis
- Hemorrhage

→

Adverse Events:

- Death
- Stroke
- Pulmonary embolism
- Heart failure
- Angina
- Myocardial infarction
- Endocarditis
- Renal insufficiency/ failure
- Reoperation
- Explantation

Questions for Panel

2. Do you agree that the device is life-supporting or presents a potential unreasonable risk of illness or injury?

Questions for Panel

- A device should be **Class I** if:
- general controls are sufficient to provide reasonable assurance of the safety and effectiveness

OR

- insufficient information exists to:
  - determine that general controls are sufficient to provide reasonable assurance of the safety and effectiveness or
  - establish special controls to provide such assurance

BUT

- is not purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, and
- does not present a potential unreasonable risk of illness or injury.

Questions for Panel

- A device should be **Class II** if:
  - general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness, AND
  - there is sufficient information to establish special controls to provide such assurance.

- A device should be **Class III** if (Section 513 of Food, Drug, and Cosmetic Act):
  - insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of its safety and effectiveness or that application of special controls would provide such assurance, AND
  - the device is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

Questions for Panel

3. FDA believes that insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of MMM allograft heart valves. Given the relative novelty of MMM processing and limited availability of clinical data, as well as the limitations of those data (e.g., only 1 cleared MMM allograft heart valve, no randomized control studies, and small patient numbers), it is challenging to draw conclusions regarding the safety and effectiveness of MMM allograft heart valves, particularly regarding their long-term performance, immunogenicity, and potential for recellularization and/or host adaptation. Consequently, FDA does not believe that special controls can be established to mitigate the known risks to health associated with these devices.

A. Do you agree with this assessment?

Questions for Panel

3. (continued)

B. If you disagree with this assessment, please identify the information you find sufficient to support a reasonable assurance of safety and effectiveness of MMM allograft heart valves when intended for use in heart valve replacement procedures.

C. In addition, please identify the special controls that could be established that you believe would be sufficient to mitigate the risks to health and provide a reasonable assurance of safety and effectiveness of MMM allograft heart valves intended for use in heart valve replacement procedures.

Questions for Panel

4. FDA believes that MMM allograft heart valves should be classified as Class III. Please indicate whether you agree with FDA's proposed classification. In accordance with 21 CFR 860.93, if you recommend a classification other than Class III for this device, please discuss the reasons for your recommendation.

Back-up slides

Section 361 criteria:

(1) The HCT/P is minimally manipulated;

(2) The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;

(3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and

(4) Either:

(i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or

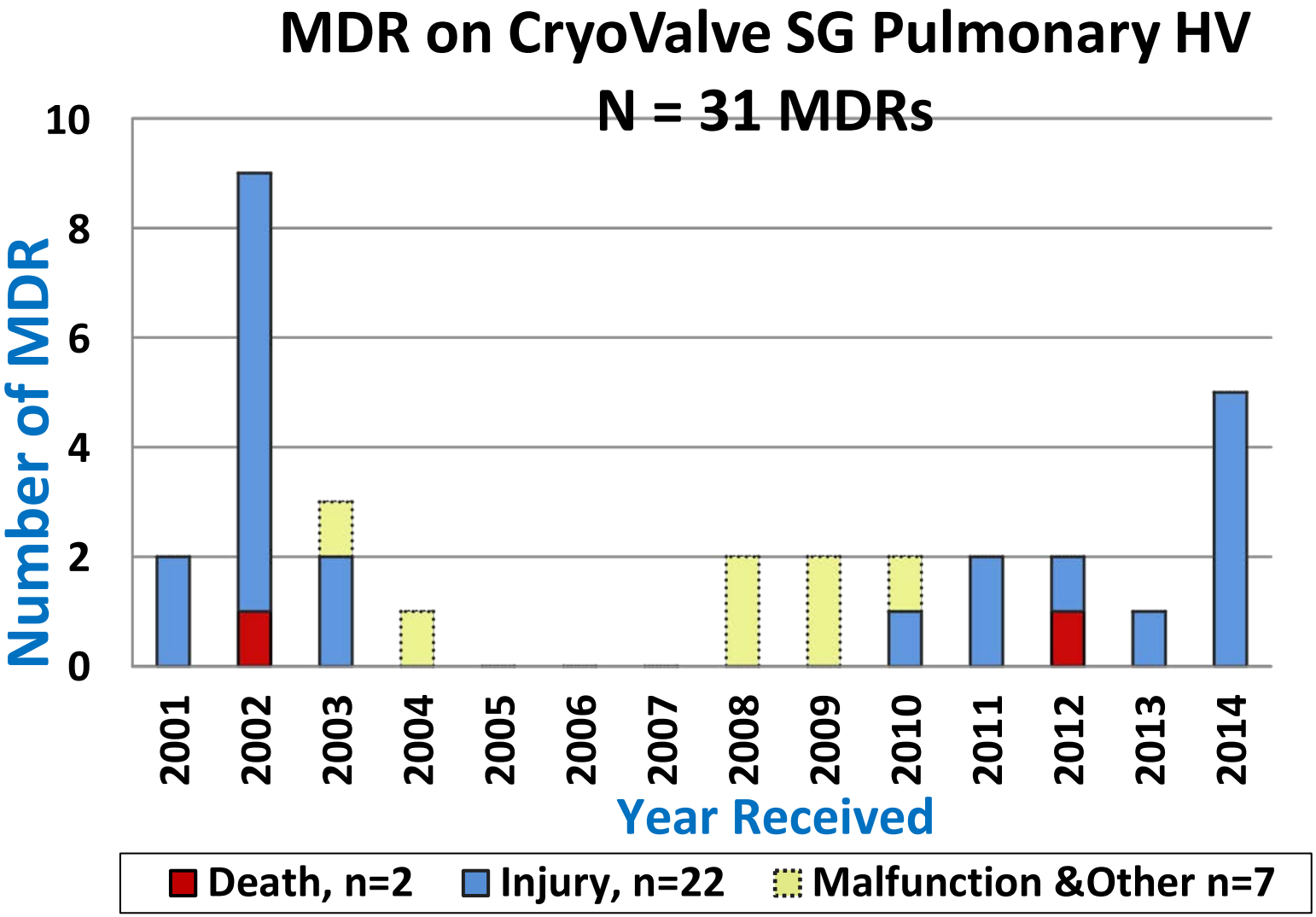
(ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:

(a) Is for autologous use;

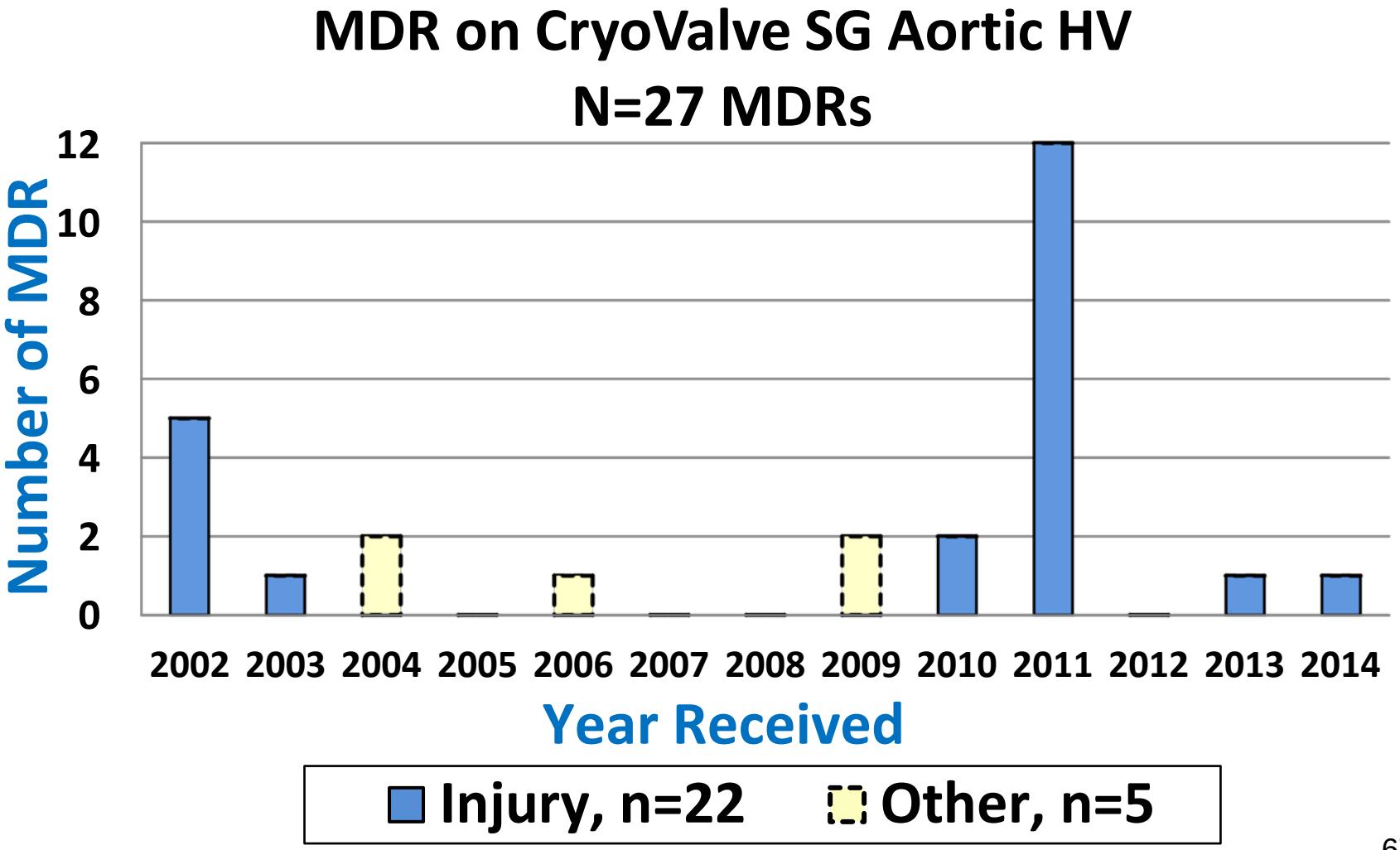
(b) Is for allogeneic use in a first-degree or second-degree blood relative; or

(c) Is for reproductive use.

MAUDE Search – Pulmonary Valve



MAUDE Search – Aortic Valve



Premarket Review of Quality System Information and Inspections

	510(k)	PMA
Statutory Authority	Under 513(f)(5) of the FD&C Act, FDA may require pre-clearance inspections for products for which there is a substantial likelihood that failure to comply with the Quality System Regulation (part 820) for such products will potentially present a serious risk to human health	Under 515(d)(2) of the FD&C Act, FDA may deny PMA approval if "the methods used in, or the facilities or controls used for, the manufacture, processing, packing or installation of such device" do not conform to the Good Manufacturing Practice Requirements (520(f)).
Premarket Review of Quality System Information	A 510(k) is not required to include quality system information. Quality system information should be maintained by the sponsor and could be reviewed during a routine or directed inspection. Quality system information is not routinely reviewed premarket.	A PMA is required to include a complete description of the methods, facilities, and controls, in sufficient detail so that FDA can make a knowledgeable assessment of the quality control used in producing the medical device. CDRH conducts a comprehensive review of the Design Controls and Manufacturing Information for compliance with 21 CFR 820, Quality System Regulation.
Premarket Inspection	A 513(f)(5) inspection may be comprehensive or more limited in scope to a specific process to ensure a finding of substantial equivalence.	Premarket inspections are routinely conducted for PMAs and include an assessment of the firm's capability to design and manufacture the device as claimed in the PMA and confirm that the firm's Quality System is in compliance with 21 CFR 820, Quality System Regulation.

Current Reports re: Decellularization

- Tsuchiya *et al.* (2014) – *Influence of pH on extracellular matrix preservation during lung decellularization.* "… the pH of the … decellularization solution influences ECM retention, cell removal, and also the potential for host response …. Preservation of ECM components, including elastin, fibronectin, and laminin, were better retained in the lower pH conditions …."

- Xu *et al.* (2014) – *Comparison of decellularization protocols for preparing a decellularized porcine annulus fibrosus scaffold*. "[two methods of decellularization] disturbed the structure of the annular fibrosus. All protocols maintained collagen content, but glycosaminoglycan content was lost to different degrees …. Furthermore, [one method] decreased the tensile mechanical property of annular fobrosus …."

- Qu *et al.* (2014) – *Decellularization of a fasciocutaneous flap for use as a perfusable scaffold.* "Despite the histological appearance of vessel integrity, none of the flaps maintained physiologic vascular integrity …."